

Pubertà precoce terapia

Aggiornamento 15 ottobre 2015

Pubertà precoce non trattata

Riduzione della statura finale

Problemi comportamentali e/o emozionali

Girls - without treatment

Reference (year)	Condition	Treatment	No. of pts	Mean target height (cm)	Mean initial predicted adult height (cm)	Mean final height (cm)
Without treatment						
Thamdrup (1961) ^[58]	CPP	None	15	NR	NR	150.5
Sigurjonsdottir (1968) ^[59]	CPP	None	21	NR	NR	153.2
Werder et al. (1974) ^[60]	CPP	None	7	161.8	NR	154.0
Lee (1981) ^[61]	CPP	None	15	164.3	156.3	155.3
Antoniazzi et al. (1994) ^[65]	CPP	None	10	156.4	NR	149.6
Kauli et al. (1997) ^[122]	CPP	None	28	159.3	161.4	155.5
Brauner et al. (1994) ^[123]	SP	None	15	161.1	162.5	162.0
Bouvattier et al. (1999) ^[124]	SP	None	10	157.8	155.2	156.1
Palmert et al. (1999) ^[67]	SP	None	20	164.0	NR	165.5
Cassio et al. (1999) ^[125]	EP	None	18	158.5	159.3	158.6

Antoniazzi F. et al. Ped Drugs 2004; 6: 221-31

Criteri

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graph TD; Criteri[Criteri] -- yellow arrow --> Test[Risposta puberale al GnRH (o GnRHa) test]; Criteri -- red arrow --> Age[Età di inizio]; Criteri -- red arrow --> Progressione[Progressione]; Criteri -- red arrow --> EO[Avanzamento EO]; Criteri -- red arrow --> Prognosis[Prognosi staturale diminuita];
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Età di inizio

Progressione

Avanzamento EO

Prognosi staturale
diminuita

Risposta puberale al GnRH
(o GnRHa) test

Table III. Suggested indications for immediate treatment with gonadotropin-releasing hormone (GnRH) agonists in children with central precocious puberty

Complete clinical precocious puberty with pubertal luteinizing hormone level after GnRH stimulation test

And

Chronological age <7y in girls and <8y in boys

Bone age advanced more than 2 SD beyond chronological age

Predicted height (by bone age and actual height) either 2 SD (10cm) or more below genetic target height or <150cm

Rapid deterioration of growth potential and rapid advancement of pubertal signs (prediction of menarche for girls aged <9y based on echographic description)

Or

Severe psychologic discomfort or behavioral reasons (individualized decision for mental retardation, emotional immaturity, and behavioral disturbances)

SD = standard deviations.

Table IV. Suggested indications for follow-up and delay in decision to treat with gonadotropin-releasing hormone (GnRH) agonists in children with central precocious puberty

Complete clinical precocious puberty with intermediate luteinizing hormone levels after the GnRH stimulation test
<i>And</i>
Chronological age between 7y and 8y in girls and between 8y and 9y in boys
Bone age advanced <2 SD beyond chronological age
Predicted height (by bone age and actual height) near target height or in the normal-to-high range
Slow progression of pubertal signs and echographic signs in girls with maintenance of a good growth potential
<i>And</i>
Absence of severe psychologic discomfort or behavioral problems
SD = standard deviations.

Progressive

Progression from one stage to the next in less than 6 mo

Accelerated

Advanced

Below target height

Uterus \geq 35 mm

Pubertal range

CPP

Pubertal stage

Growth velocity

Bone age

Height prognosis

Pelvic sonography

LH peak after GnRH

Slowly progressive

Stabilisation or regression of pubertal signs

Normal for age

Variable

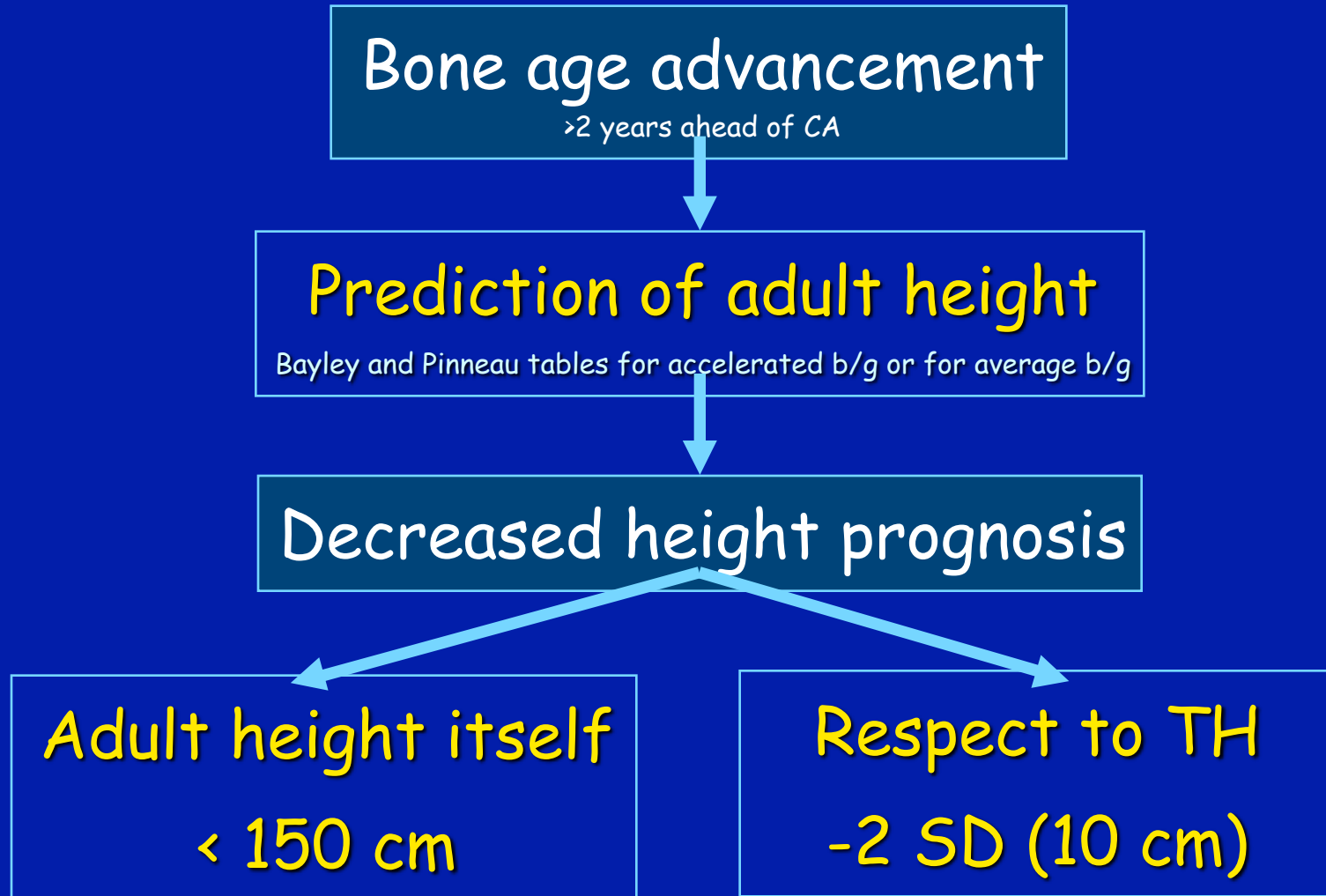
Within target height

Uterus \leq 35 mm

Prepubertal range

Follow-up

Criteria to treat - Auxology



Scopi della terapia

Inibire la pubertà

Arrestare la progressione dei segni puberali
secondari o le mestruazioni

Ritardare la chiusura delle cartilagini di coniugazione
- aumentare la statura finale

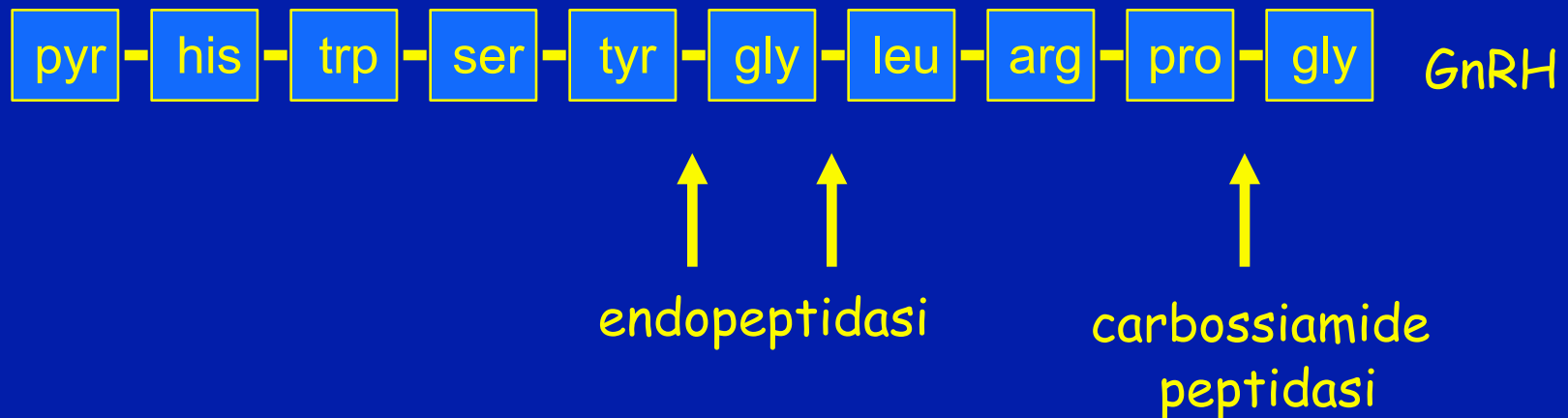
Migliorare il benessere psicologico

Trattare le eventuali cause sottostanti

Come e con che cosa trattare?..

Effetti delle sostituzioni aminoacidiche dei GnRH agonisti

- maggiore affinità per i recettori del GnRH
- resistenza alla azione delle proteasi e più lunga emivita plasmatica



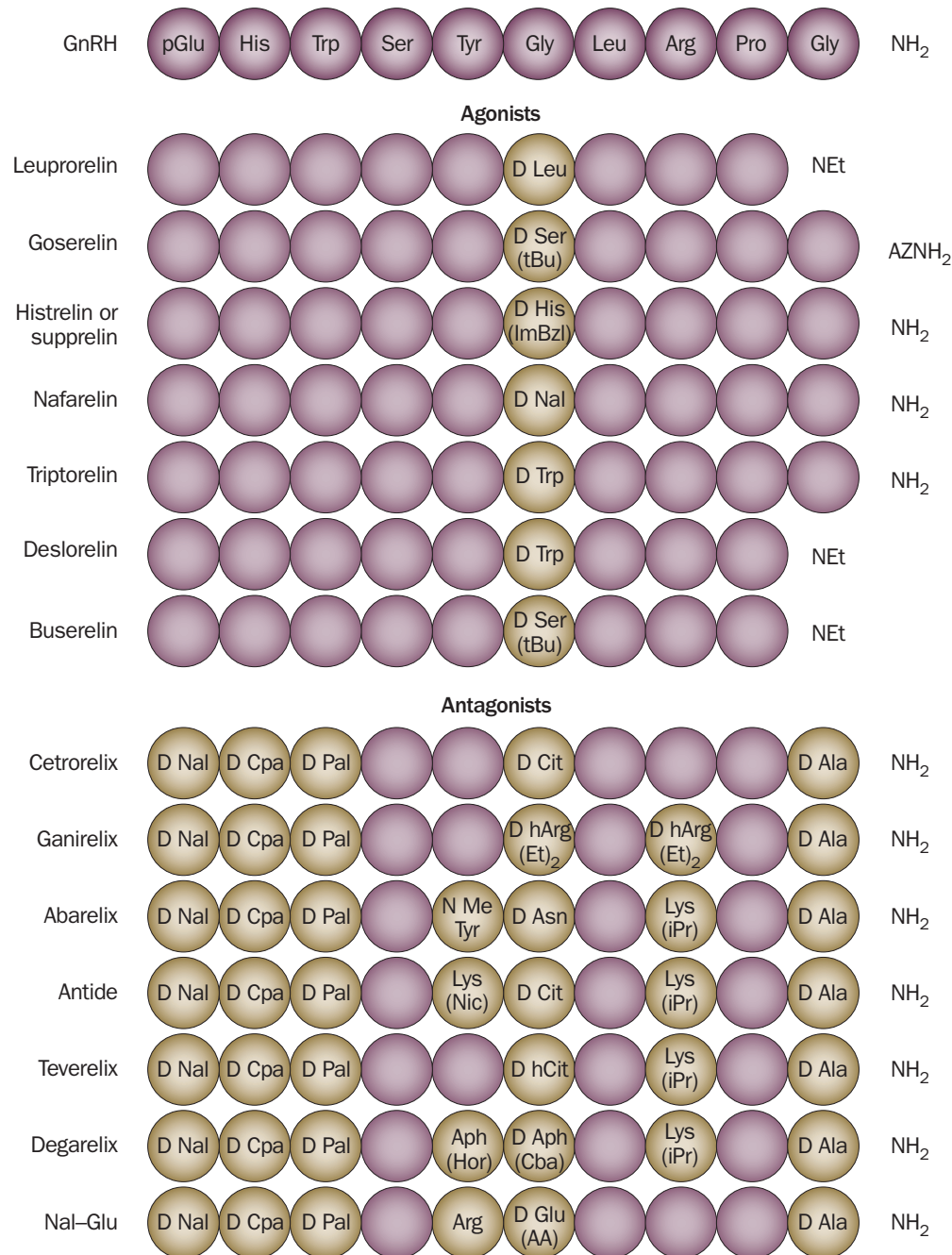
Current and future applications of GnRH, kisspeptin and neurokinin B analogues

Robert P. Millar and Claire L. Newton

Abstract | Reproductive hormones affect all stages of life from gamete production, fertilization, fetal development and parturition, neonatal development and puberty through to adulthood and senescence. The reproductive hormone cascade has, therefore, been the target for the development of numerous drugs that modulate its activity at many levels. As the central regulator of the cascade, gonadotropin-releasing hormone (GnRH) agonists and antagonists have found extensive applications in treating a wide range of hormone-dependent diseases, such as precocious puberty, prostate cancer, benign prostatic hyperplasia, endometriosis and uterine fibroids, as well as being an essential component of *in vitro* fertilization protocols. The neuroendocrine peptides that regulate GnRH neurons, kisspeptin and neurokinin B, have also been identified as therapeutic targets, and novel agonists and antagonists are being developed as modulators of the cascade upstream of GnRH. Here, we review the development and applications of analogues of the major neuroendocrine peptide regulators of the reproductive hormone cascade: GnRH, kisspeptin and neurokinin B.

Millar, R. P. & Newton, C. L. *Nat. Rev. Endocrinol.* advance online publication 2 July 2013; doi:10.1038/nrendo.2013.120

Figure 3 | GnRH agonist and antagonist peptide analogues in clinical practice or in clinical development. The mammalian GnRH sequence is shown above in purple circles and substitutions shown in brown circles. All analogues have a D-amino acid substitution in position 6 to enhance the folding of the molecule and increase binding affinity and decrease degradation. Carboxyl terminal substitutions further decrease degradation. All antagonists have substitutions in the amino terminal domain, which ablates receptor activation. Abbreviation: GnRH, gonadotropin-releasing hormone. Permission to adapt obtained from The Endocrine Society © Millar, R. P. *et al.* Gonadotropin-releasing hormone receptors. *Endocr. Rev.* **25**(2), 235–275 (2004).³ <http://edrv.endojournals.org/>



Current and future applications of GnRH, kisspeptin and neurokinin B analogues

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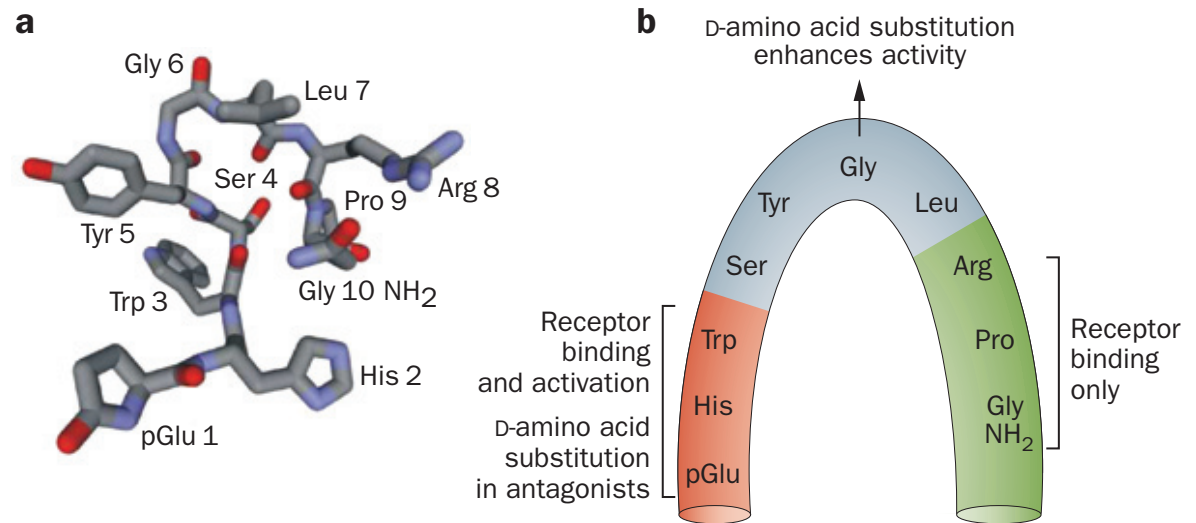


Figure 2 | The 3D structure of GnRH. **a** | NMR structure of mammalian GnRH showing the β -II' bend around glycine in position 6. The β -II' type turn occurs when a region of the peptide involving four consecutive amino acids folds back on itself by nearly 180°. **b** | Schematic representation of mammalian GnRH in the folded conformation, in which it is bound to the GnRH pituitary receptor. The molecule is bent around the achiral glycine in position 6. Substitution with D-amino acids in this position stabilizes the folded conformation, increases binding affinity and decreases metabolic clearance. This feature is incorporated in all agonist and antagonist analogues. The amino (red) and carboxyl (green) termini are involved in receptor binding. The amino terminus alone is involved in receptor activation and substitutions in this region produce antagonists. Abbreviation: GnRH, gonadotropin-releasing hormone. Part a reprinted from *Front. Neuroendocrinol.* **29** (1), Millar, R. P. *et al.* Diversity of actions of GnRHs mediated by ligand-induced selective signaling, 17–35, © 2007, with permission from Elsevier.⁵² Part b adapted from Millar, R. P. in *Reproductive Medicine: Molecular, Cellular and Genetic Fundamentals* (ed. Fauser, B. C. J. M.) (Parthenon Publishing, Lancaster, 2002).

Conseguenze delle sostituzioni aminoacidiche sulla potenza e stabilità dei GnRH agonisti

- rispetto al GnRH nativo gli analoghi hanno:
 - maggiore affinità di legame per i recettori del GnRH
 - rallentata dissociazione dai recettori del GnRH
 - più lenta degradazione da parte delle proteasi plasmatiche
- da questo consegue una maggiore potenza ed una più prolungata attività biologica

Meccanismo di azione dei GnRH agonisti

- fase stimolatoria
 - durata: 1 - 2 settimane
 - induce elevate concentrazioni di gonadotropine e steroidi gonadici
- fase soppressiva
 - segue la fase stimolatoria
 - produce bassi livelli di gonadotropine e steroidi gonadici
 - provoca l'arresto della maturazione follicolare nella donna e della spermatogenesi nell'uomo
 - dura fino alla sospensione della somministrazione dei GnRH analoghi

Caratteristiche farmacologiche dei GnRH agonisti

- selettività e specificità del meccanismo di azione
- efficacia assoluta
- reversibilità completa
- assenza di effetti collaterali diretti

Effetti collaterali dei GnRH agonisti

- effetti collaterali diretti
 - nessuno
- effetti collaterali indiretti (tutti legati al blocco della secrezione ormonale gonadica)
 - vampate di calore
 - insonnia
 - labilità emotiva
 - emicranie
 - osteopenia (potenziale)

Razionale per la terapia con GnRH agonisti

- La somministrazione acuta stimola la secrezione delle gonadotropine ipofisarie
- La somministrazione cronica desensibilizza i recettori per il GnRH sulle cellule gonadotrope ipofisarie, come farebbe una infusione costante ev di GnRH naturale

Formulazioni dei GnRH agonisti

Via di somministrazione	frequenza di somministrazione	assorbimento
Intranasale	ogni 6 -8 ore	scarso (< 3 %)
Sottocutanea	ogni 12 - 24 ore	buono
Depot intramuscolari e sottocutanei	ogni 28 giorni (ogni 3 mesi)	buono

Agonisti del GnRH usati nel trattamento della pubertà precoce vera

agonista	via di somministrazione	dose
Buserelin	sottocutanea	20-40 $\mu\text{g/kg/die}$ in 2 dosi
	intranasale	1200-1800 $\mu\text{g/die}$ in 3 dosi
Leuprolide	sottocutanea	40-50 $\mu\text{g/kg/die}$ in 2 dosi
	intramuscolare depot	100-200 $\mu\text{g/kg}$ ogni 21-28 gg
Triptorelin	intramuscolare depot	60-120 $\mu\text{g/kg}$ ogni 21-28 gg

Medications Used for the Treatment of Precocious Puberty

Table 4. Medications Used for the Treatment of Precocious Puberty.*

Drug	Formulation and Usually Recommended Dose	Side Effects and Cautions
For treatment of central or gonadotropin-dependent precocious puberty		
Depot GnRH agonists†		
Overview		Local side effects include pain, erythema, inflammatory reaction, sterile abscess, implant-site reaction; other side effects include headaches and menopausal-like symptoms (hot flashes, asthenia); decreased bone density during treatment but no long-term impairment documented after treatment is discontinued
Leupronel in leuprolide (Eli Lilly) [Takeda], Lupron Depot [TAP], Lupron Depot-PED [TAP]‡	4-wk and 12-wk preparations (subcutaneous or intramuscular); United States — 0.3 mg/kg of body weight every 4 wk (1-mo depot); Europe — 3.75 mg every 4 wk (4-wk depot) or 11.25 mg every 12 wk (12-wk depot)	
Triptorelin (Decapeptyl [Ipser, Ferring], Gonapeptyl [Ferring])§	4-wk and 12-wk preparations (intramuscular); Europe — 3.00–3.75 mg every 4 wk (1-mo depot) or 11.25 mg every 12 wk (1-mo depot)	
Goserelin (Zoladex [AstraZeneca], 3.6 mg or 10.8 mg)	4-wk and 12-wk implants	
Histrelin (Supprelin LA [Indevus])	12-mo implants United States — 50-mg implant every 12 mo	
Rapid-acting GnRH agonists — buserelin, deslorelin, histrelin, leupronel, leuprolide, nafarelin, triptorelin	Nasal spray or subcutaneous injections 1–3 times daily	Difficulties with compliance; use usually limited to patients with sterile abscesses from depot injections
For treatment of peripheral or gonadotropin-independent precocious puberty¶		
Aromatase inhibitors		
Testolactone (Teslac [Bristol-Myers Squibb])	40 mg/kg of body weight/day orally, 4–6 times daily	Data from small, uncontrolled trials in McCune-Albright syndrome; also used in association with spiroglactone for familial male-limited precocious puberty ²⁰
Letrozole (Femara [Novartis])	2.5 mg orally once daily	Menopause-like symptoms; data from small, uncontrolled trial in McCune-Albright syndrome ²¹
Anastrozole (Arimidex [AstraZeneca])	1 mg orally once daily	Data from case reports
SERM — Tamoxifen (Nolvadex [AstraZeneca])	20 mg orally once daily	Data from small, uncontrolled trials in McCune-Albright syndrome ²²
Androgen-synthesis inhibitor — ketoconazole (Nizoral [Janssen-Cilag])	20 mg/kg of body weight/day orally	Side effects include liver toxicity and adrenal deficiency; data from small, uncontrolled trials in familial male-limited precocious puberty ²³

* Drugs used for the treatment of adrenal disorders (congenital adrenal hyperplasia) are not included in this table. SERM denotes selective estrogen-receptor modulators.

† The availability, approval for use, and recommended dosages of depot GnRH agonists for the treatment of precocious puberty vary throughout the world.

‡ The Food and Drug Administration has approved Lupron Depot-PED and Supprelin LA for the treatment of central precocious puberty. Histrelin implants are available only in the United States.

§ Triptorelin is not available in the United States.

¶ None of these drugs have been approved for use in the treatment of precocious puberty.

Follow-up

In terapia:

peso, altezza e segni clinici	ogni 3 mesi
GnRH ev o sc:	in caso di scarso controllo
Ecografia pelvica (F):	ogni 6 mesi
Rx età ossea:	ogni anno

Segni di buona soppressione:

Steroidi sessuali:	Testosterone (M):	< 45 ng/dl
	Estradiolo (F):	< 9 pg/ml,
Gonadotropine:	LH	< 2.0 IU/l

$\Delta BA / \Delta CA < 1$ è un criterio secondario

Stop terapia ai 12 anni di età ossea

Follow-up post terapia

Dopo stop terapia:

Peso e altezza e segni clinici ogni 6 mesi

Registrazione menarca (F)

Statura definitiva, notizie riguardanti il ciclo (F)

Carico GnRH ev o sc:

inizialmente ogni 6 mesi fino al raggiungimento di un profilo pubere

Ecografia pelvica:

ogni 6 mesi fino al raggiungimento di un quadro pubere

Girls - GnRHa treatment (nasal - sc)

				TH	PH	FH
GnRH agonists (daily SC or EN)						
Boepple et al. (1991) ^[126]	CPP	Deslorelin/histrelin SC	27	NR	147.5	149.9
Antoniuzzi et al. (1994) ^[85]	CPP	Buserelin EN	15	155.5	152.9	153.2
Cacciari et al. (1994) ^[79]	CPP	Buserelin EN	12	162.5	156.7	159.5
Klein et al. (2001) ^[127]	CPP	Deslorelin/histrelin SC	80	163.7	149.3	159.8

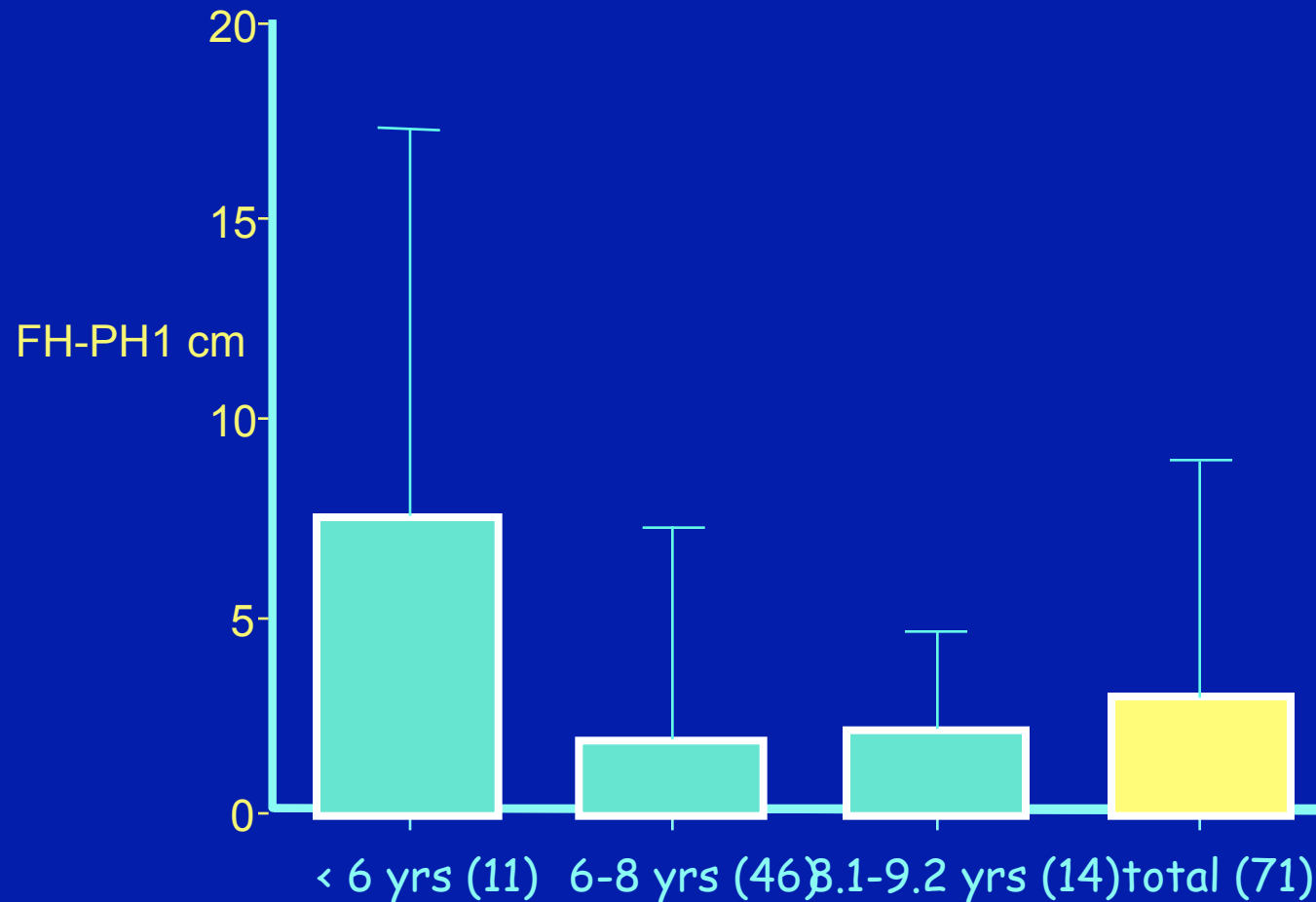
Antoniuzzi F. et al. Ped Drugs 2004; 6: 221-31

Girls - GnRHa treatment (depot)

				TH	PH	FH
GnRH agonists (depot IM or SC)						
Brauner et al. (1994) ^[123]	CPP	Triptorelin	19	160.2	152.0	159.0
Antoniuzzi et al. (1994) ^[85]	CPP	Triptorelin	15	157.6	154.1	160.6
Kauli et al. (1997) ^[122]	CPP	Triptorelin	48	157.7	154.4	159.6
Bertelloni et al. (1998) ^[128]	CPP	Buserelin/ triptorelin	14	161.0	153.5	158.1
Galluzzi et al. (1998) ^[129]	CPP	Triptorelin	22	163.5	155.2	158.5
Arrigo et al. (1999) ^[108]	CPP	Triptorelin	71	161.5	155.5	158.4
Carel et al. (1999) ^[107]	CPP	Triptorelin	58	160.1	156.4	161.1
Heger et al. (1999) ^[112]	CPP	Triptorelin	50	163.6	154.9	160.6
Mul et al. (2000) ^[130]	CPP	Triptorelin	87	168.0	155.3	162.5
Bouvattier et al. (1999) ^[124]	EP	Triptorelin	20	157.6	154.1	157.6
Cassio et al. (1999) ^[125]	EP	Triptorelin	20	157.0	157.8	158.1

Antoniuzzi F. et al. Ped Drugs 2004; 6: 221-31

FH-PH1 after GnRHa treatment



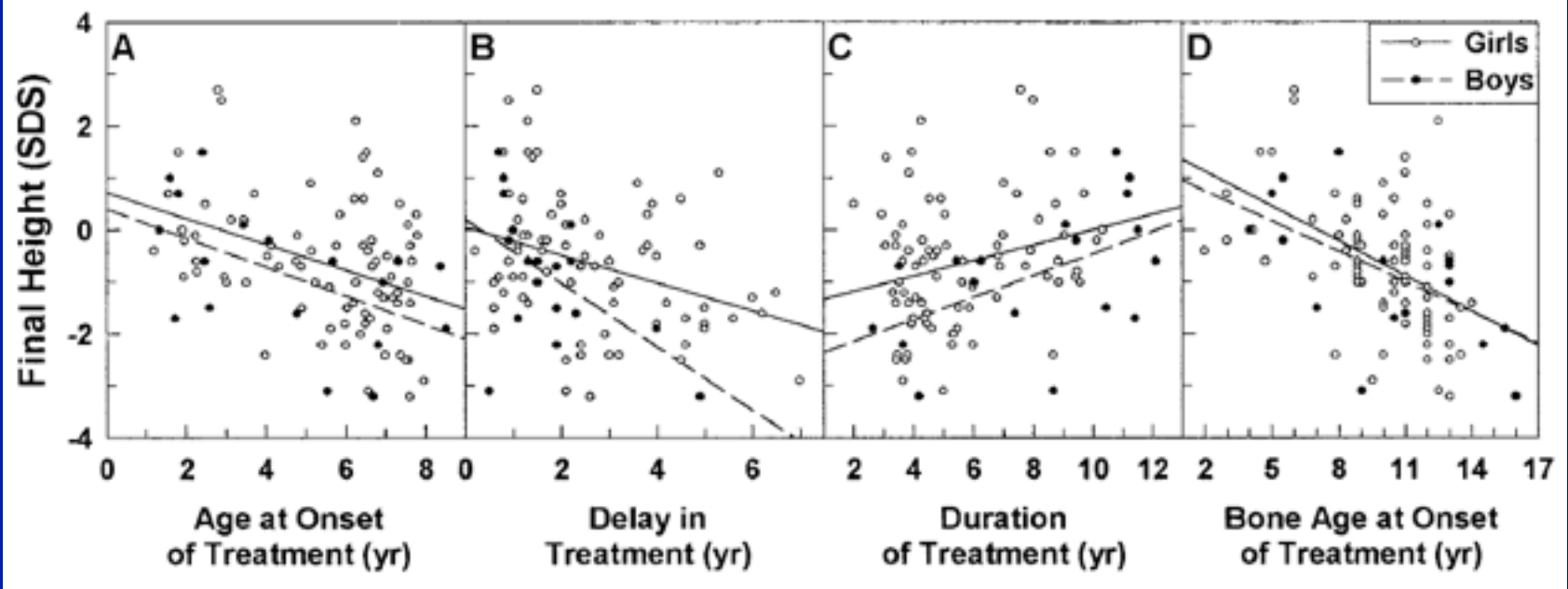
Arrigo T et al. Eur J Endocrinol 1999; 141: 140

Boys

		pts	Target height (cm)	predicted adult height (cm)	Final height (cm)
Without treatment					
Thamdrup (1961) ^[58]	None	8	NR	NR	155.4
Sigurjonsdottir (1968) ^[59]	None	14	NR	NR	156.1
GnRH agonists (daily SC or EN)					
Paul et al. (1995) ^[131]	Nafarelin/ deslorelin/ leuprolide (leuprorelin)((Author: SC or EN?))	6	180.0	161.3	168.0
Klein et al. (2001) ^[127]	Deslorelin/histrelin SC	18	178.3	156.1	171.1
GnRH agonists (depot IM or SC)					
Galluzzi et al. (1998) ^[129]	Triptorelin	11	174.5	168.3	175.5
Rizzo et al. (2000) ^[132]	Buserelin/ triptorelin	12	174.2	169.9	176.1
Lazar et al. (2001) ^[71]	Triptorelin	11	170.6	174.0	172.5
Mul et al. (2002) ^[133]	Triptorelin	26	NR	NR	172.9

EN = endonasal; IM = intramuscular; NR = not reported; pts = patients; SC = subcutaneous.

Antoniazzi F. et al. Ped Drugs 2004; 6: 221-31



NIH Oerter-Klein K et al. JCE&M 2001; 86: 4711-6

Gonadotropin Releasing Hormone Agonist Treatment to Increase Final Stature in Children With Precocious Puberty

A Meta-Analysis

Pin Li, PhD, MD, Yan Li, MD, and Chung-Lin Yang, MS

Medicine • Volume 93, Number 27, December 2014

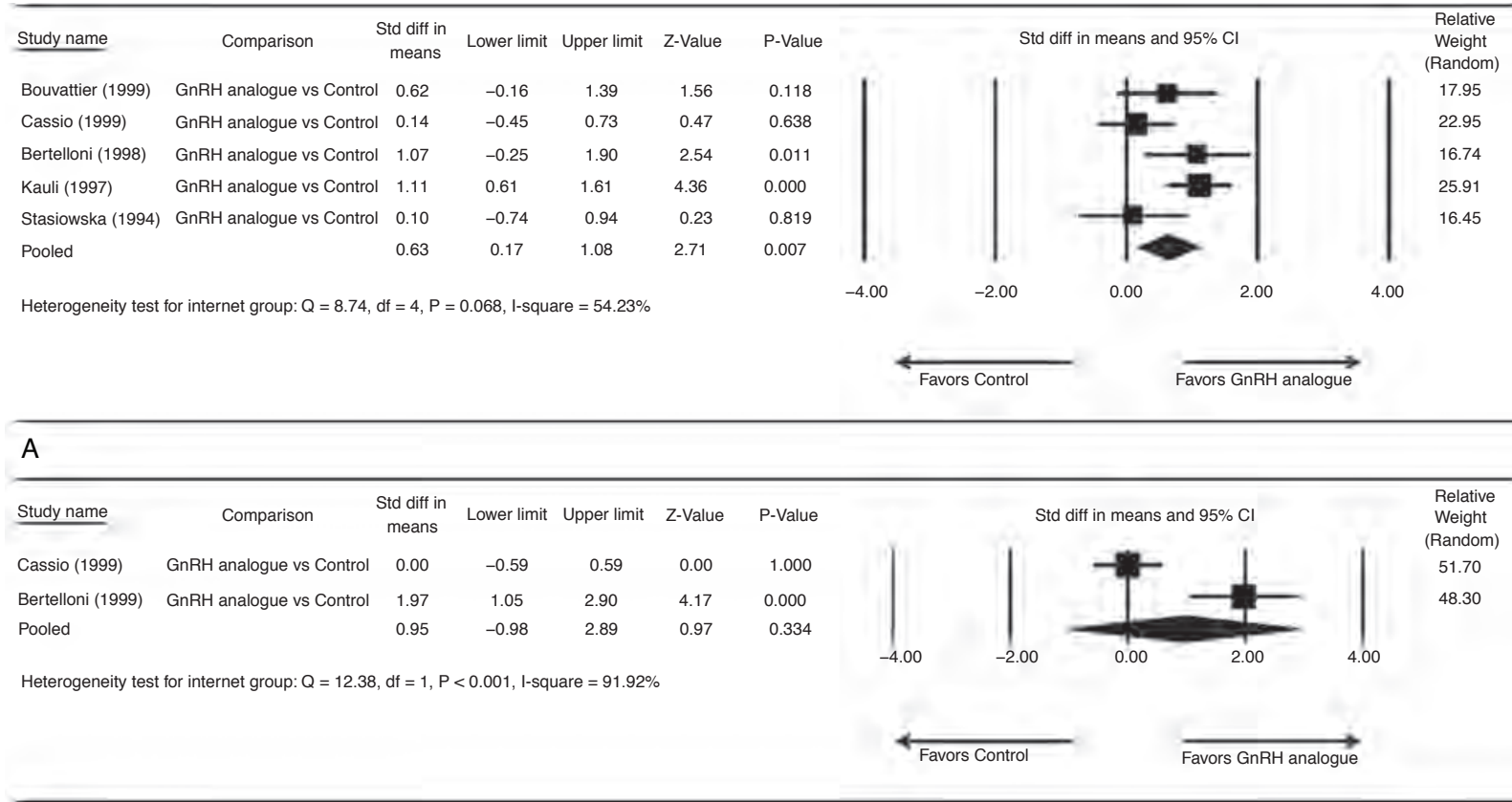


FIGURE 3. Forest plots showing results for the meta-analysis of (A) difference between final height and predicted adult height; (B) difference between final height SDS and initial height SDS for GnRH analogue group compared to the control group. CI = confidence interval.

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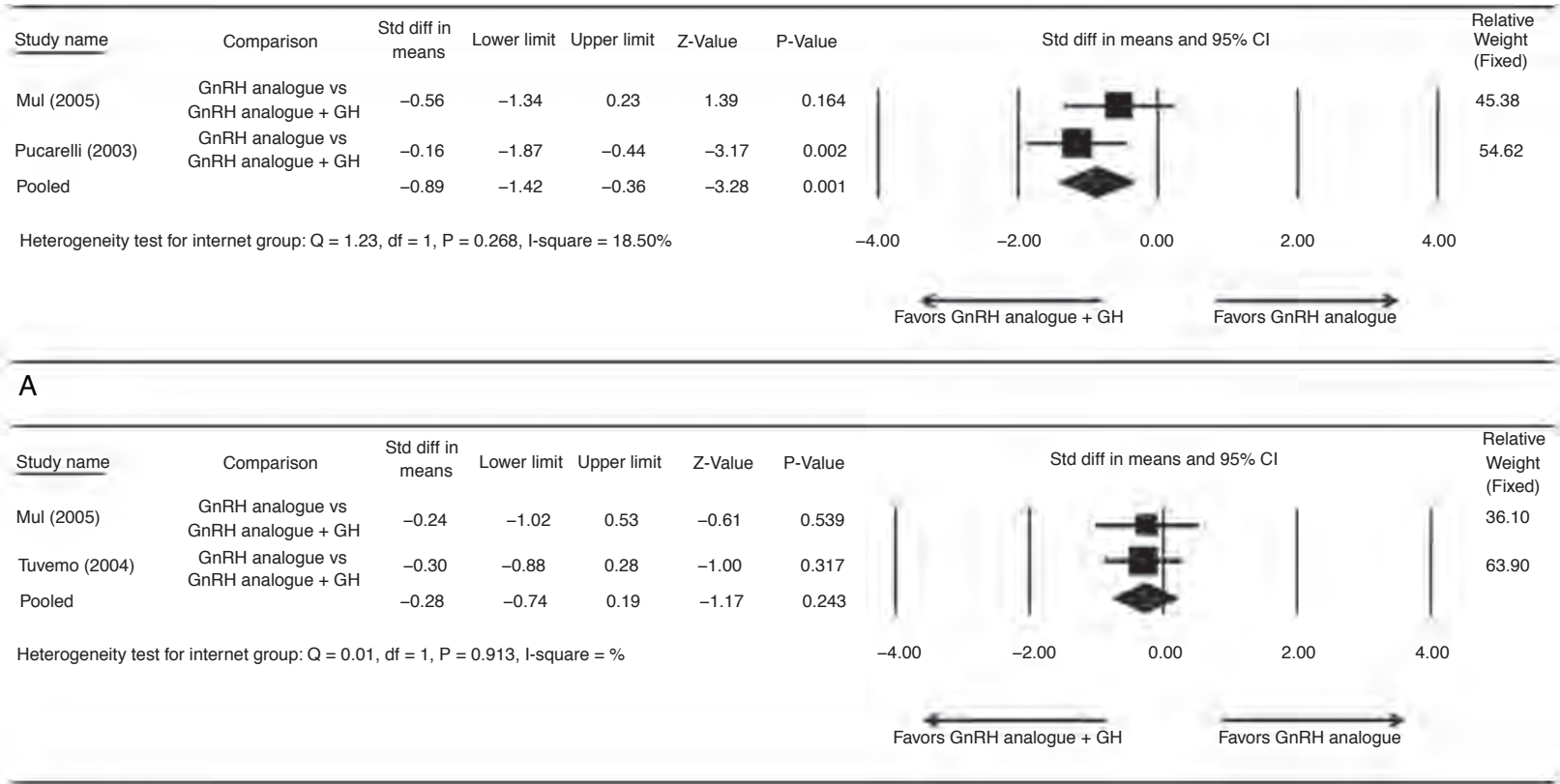


FIGURE 4. Forest plots showing results for the meta-analysis of (A) difference between final height and predicted adult height; (B) difference between final height SDS and initial height SDS incidence for GnRH analogue group compared with the GnRH analogue plus GH group. CI = confidence interval.

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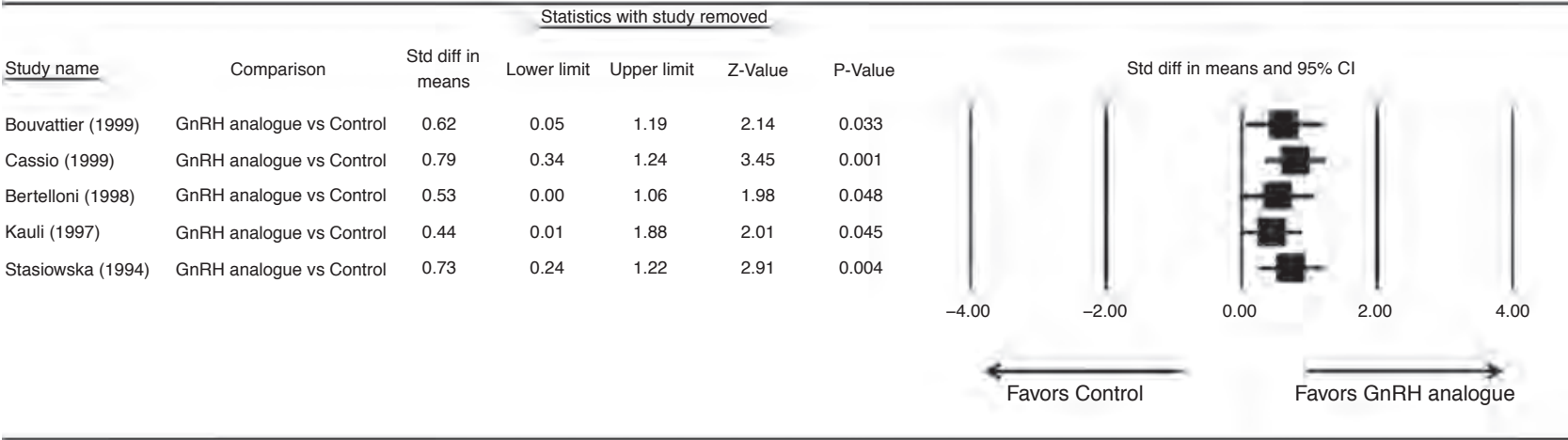


FIGURE 5. Results of sensitivity analysis to examine the influence of individual studies on pooled estimates as determined use the leave-one-out approach of difference between final height and predicted adult height for GnRH analogue group compared to the control group. CI = confidence interval, OR = odds ratio.

Il trattamento migliora la statura?

Si, se utilizzato:

Precocemente

Età cronologica

Età ossea

Per tempi corretti

Previsione di statura

Pros and cons of GnRHa treatment for early puberty in girls

Ruben H. Willemsen, Daniela Elleri, Rachel M. Williams, Ken K. Ong and David B. Dunger

Nat. Rev. Endocrinol. 10, 352–363 (2014)

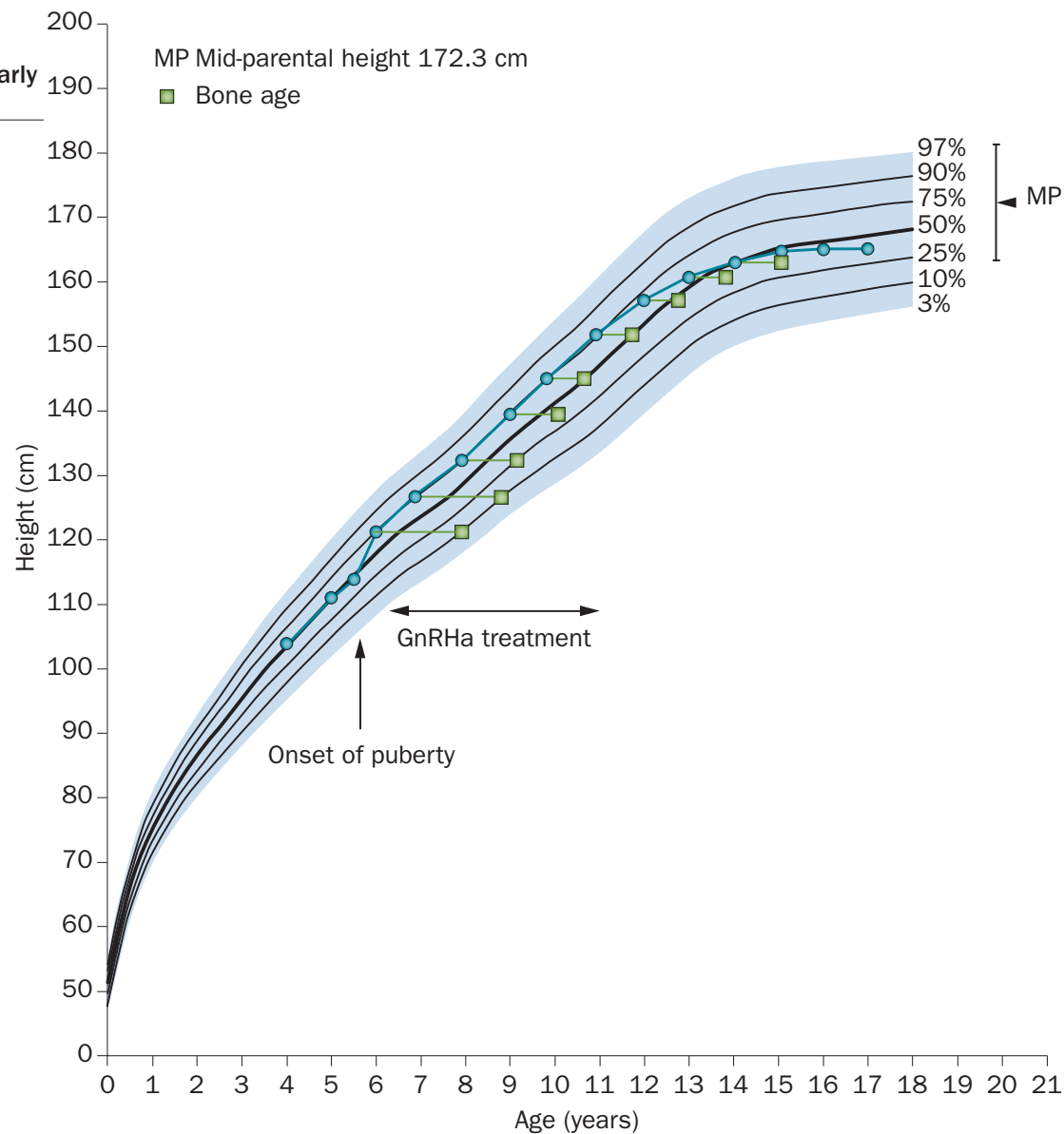


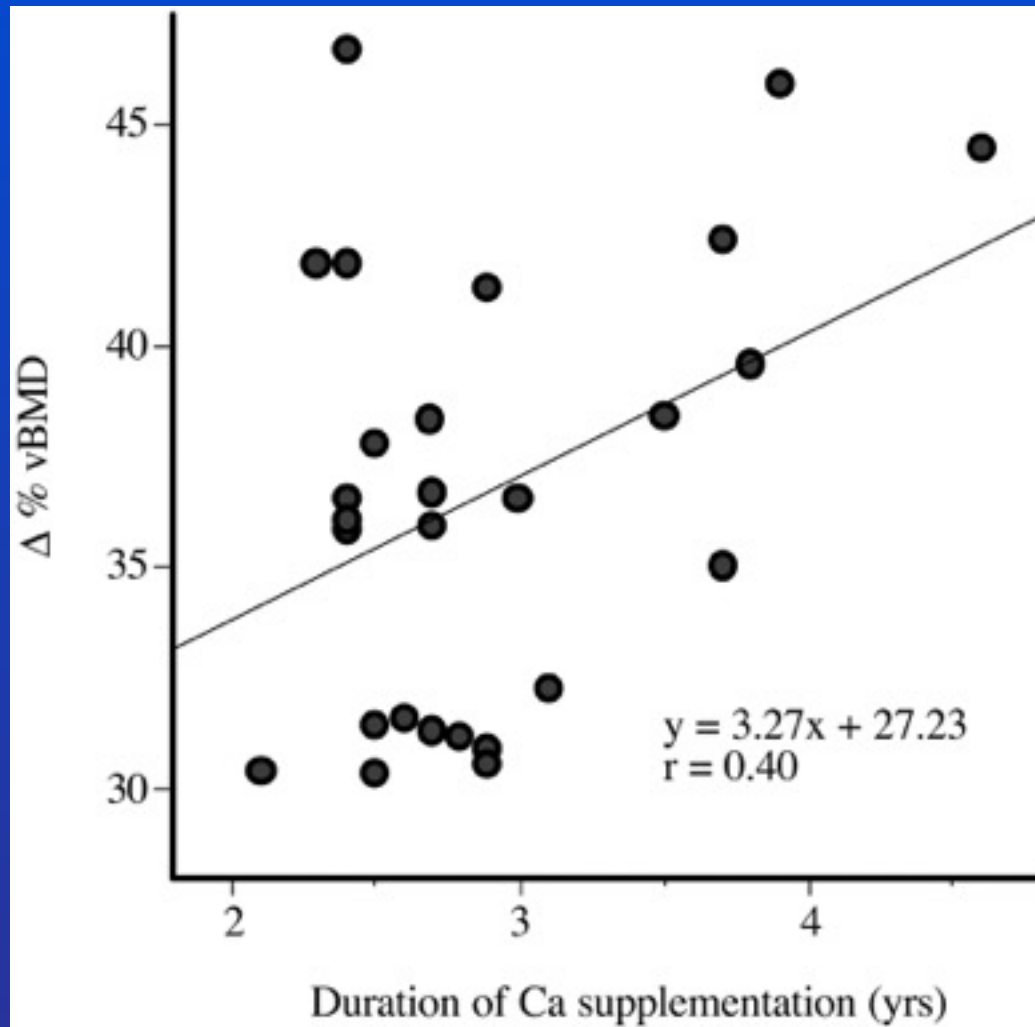
Figure 2 | Typical treatment with GnRHa. Delaying puberty with GnRHa treatment results in prolongation of prepubertal height gain and slowing down of bone age advancement leading to greater gains in height before epiphyses fuse.

Il trattamento influenza la
composizione corporea?

Probabilmente no!

Dati contrastanti

Esiste una associazione più frequente
tra sovrappeso o obesità
e precocità puberale



Antoniazzi, F. et al. J Clin Endocrinol Metab 2003;88:1096-1101

Il trattamento influenza
il Peak Bone Mass?

No

Meglio non avere
altri fattori aggiuntivi di
rischio

Current pharmacotherapy of central precocious puberty by GnRH analogs: certainties and uncertainties

Silvano Bertelloni[†] & Giampiero I Baroncelli

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Expert Opin. Pharmacother. (2013) **14**(12)

Long-acting and very long-acting GnRH analogs are the treatment of choice for children with CPP.

Long-term therapeutic goals are the improvement of adult height and minimizing psychosocial disturbances (if present).

Several studies demonstrated the benefit of monthly GnRH analog on long-term outcome, but criteria to start, monitor and discontinue therapy remain to be better defined.

Very long-term (quarterly and yearly) GnRH analogs represent a key developmental step in improving the medical treatment of CPP, but longer follow-up and comparative trials among the various drugs should be done.

No serious adverse effects on reproductive axis, body composition and bone health of GnRH analog treatment for CPP have been reported, but surveillance studies till late adulthood should be encouraged.

Children with CPP should be managed regarding GnRH analog treatment (if needed) and followed by pediatric endocrinologists with documented experience in this field.

Conclusioni (1)

- La maggior parte delle bambine trattate per Pubertà Precoce può raggiungere una statura finale nella norma e/o il target genetico
- Il trattamento andrebbe iniziato il più presto possibile e terminato ad una età ossea di 12-12.5 anni
- Alla fine del trattamento vi è un pronto recupero della funzione dell'asse ipotalamo-ipofisi-gonadi
- Il trattamento con GnRHa non impedisce il raggiungimento di un normale picco di massa ossea adolescenziale

Conclusioni (2)

- In generale vi sono buoni risultati con la terapia con GnRH agonisti
- Le formulazioni ritardo sono più efficaci nel controllo della pubertà e per una statura finale migliore
- In casi selezionati associazione con GH o oxandrolone
- Il trattamento non causa (e non aggrava) l'obesità (?)
- Rimangono da stabilire vantaggi e svantaggi sulla evoluzione psicologica

Conclusioni (3)

Indicazioni suggerite per il trattamento con
GnRH agonisti

Abnormale potenziale di crescita

Perdita significativa di statura finale predetta

Statura finale predetta < al 5° centile

Coesistenza di deficit di GH

Sulla base di problemi psicosociali o individuali

Mestruazioni in immaturità mentale o psicologica

Disturbi comportamentali o emozionali

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Key points

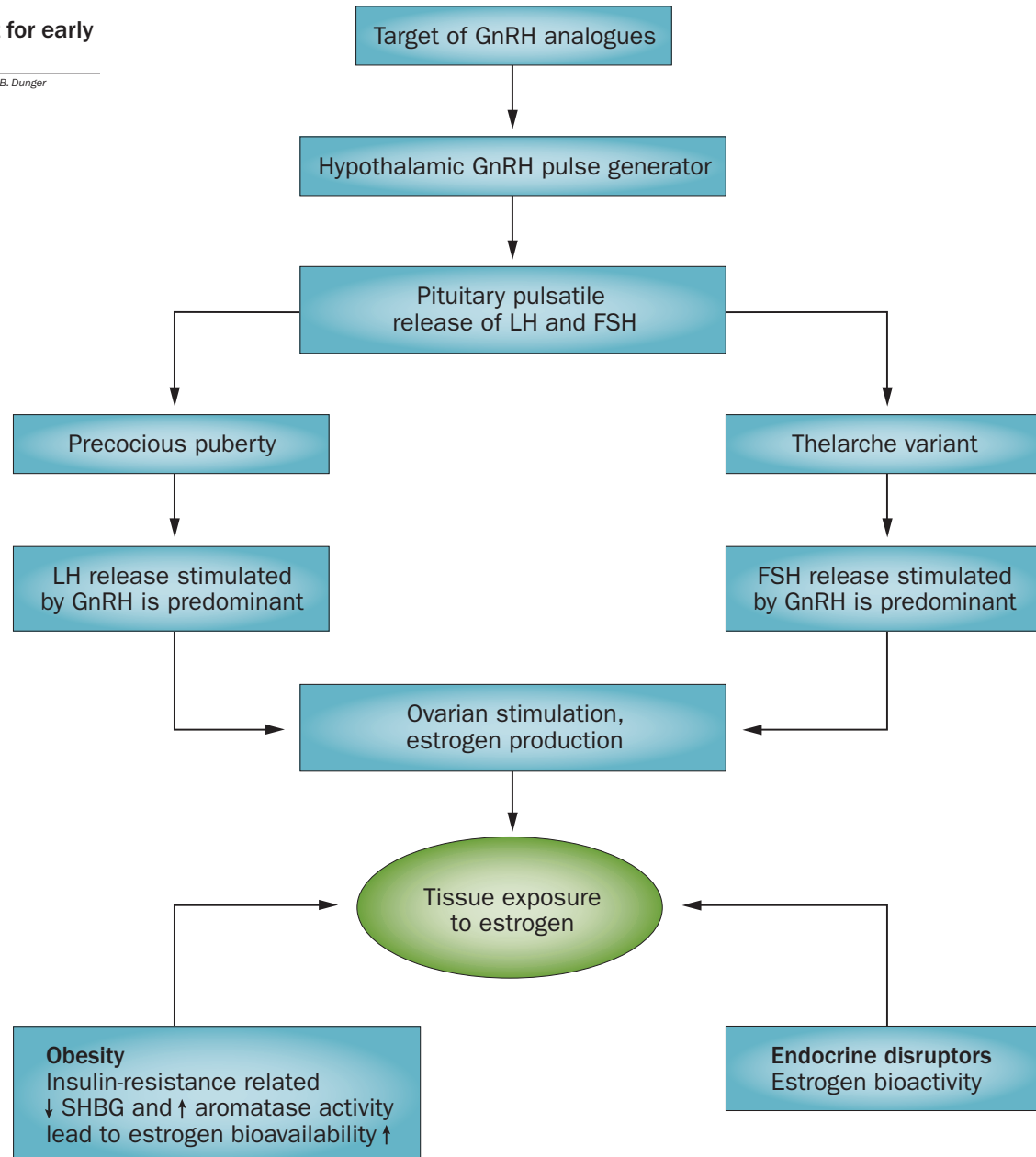
- Secular trends in age at pubertal development and the potential influence of environmental factors challenge the standard definitions of precocious puberty and the indications for intervention with gonadotropin-releasing hormone agonists (GnRHa)
- Treatment with GnRHa can improve adult height in patients who present with precocious puberty at a young age, without having adverse effects
- Whether GnRHa therapy is beneficial for patients with atypical forms of early puberty not driven by luteinising hormone is unknown
- Early exposure to estrogen (at <8 years old) might have long-term implications for adult health, such as increasing the risks of developing breast cancer, the metabolic syndrome and type 2 diabetes mellitus
- Alternative intervention strategies need to be evaluated in girls with early puberty, such as weight loss or therapy with insulin sensitizers

REVIEWS

Pros and cons of GnRHa treatment for early puberty in girls

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Problemi psicologici

Valutare da caso a caso

Particolare attenzione ai ritardi psicomotori

Attenzione a non trasformare un evento
precoce in una "malattia"

Current and future applications of GnRH, kisspeptin and neurokinin B analogues

Robert P. Millar and Claire L. Newton

Abstract | Reproductive hormones affect all stages of life from gamete production, fertilization, fetal development and parturition, neonatal development and puberty through to adulthood and senescence. The reproductive hormone cascade has, therefore, been the target for the development of numerous drugs that modulate its activity at many levels. As the central regulator of the cascade, gonadotropin-releasing hormone (GnRH) agonists and antagonists have found extensive applications in treating a wide range of hormone-dependent diseases, such as precocious puberty, prostate cancer, benign prostatic hyperplasia, endometriosis and uterine fibroids, as well as being an essential component of *in vitro* fertilization protocols. The neuroendocrine peptides that regulate GnRH neurons, kisspeptin and neurokinin B, have also been identified as therapeutic targets, and novel agonists and antagonists are being developed as modulators of the cascade upstream of GnRH. Here, we review the development and applications of analogues of the major neuroendocrine peptide regulators of the reproductive hormone cascade: GnRH, kisspeptin and neurokinin B.

Millar, R. P. & Newton, C. L. *Nat. Rev. Endocrinol.* advance online publication 2 July 2013; doi:10.1038/nrendo.2013.120

Figure 1 | The reproductive hormone cascade and therapeutic analogues that target the cascade. The figure shows the diverse internal and external factors regulating brain neuroendocrine neuropeptides, which in turn regulate downstream GnRH, pituitary gonadotropins and gonadal hormones. Positive and negative feedback by gonadal steroids and peptides is also shown. Analogues have been developed that target all levels of the cascade. Those in clinical use are highlighted in red boxes, those in purple boxes are being developed but are not yet in clinical use. Abbreviations: FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; GnIH, gonadotropin-inhibitory hormone; LH, luteinizing hormone; MSH, melanocyte-stimulating hormone.

